
# Early Detection Research Network (EDRN)

## A National Infrastructure for Biomarker Development

*Pre-Application Meeting for **RFA-CA-16-009***
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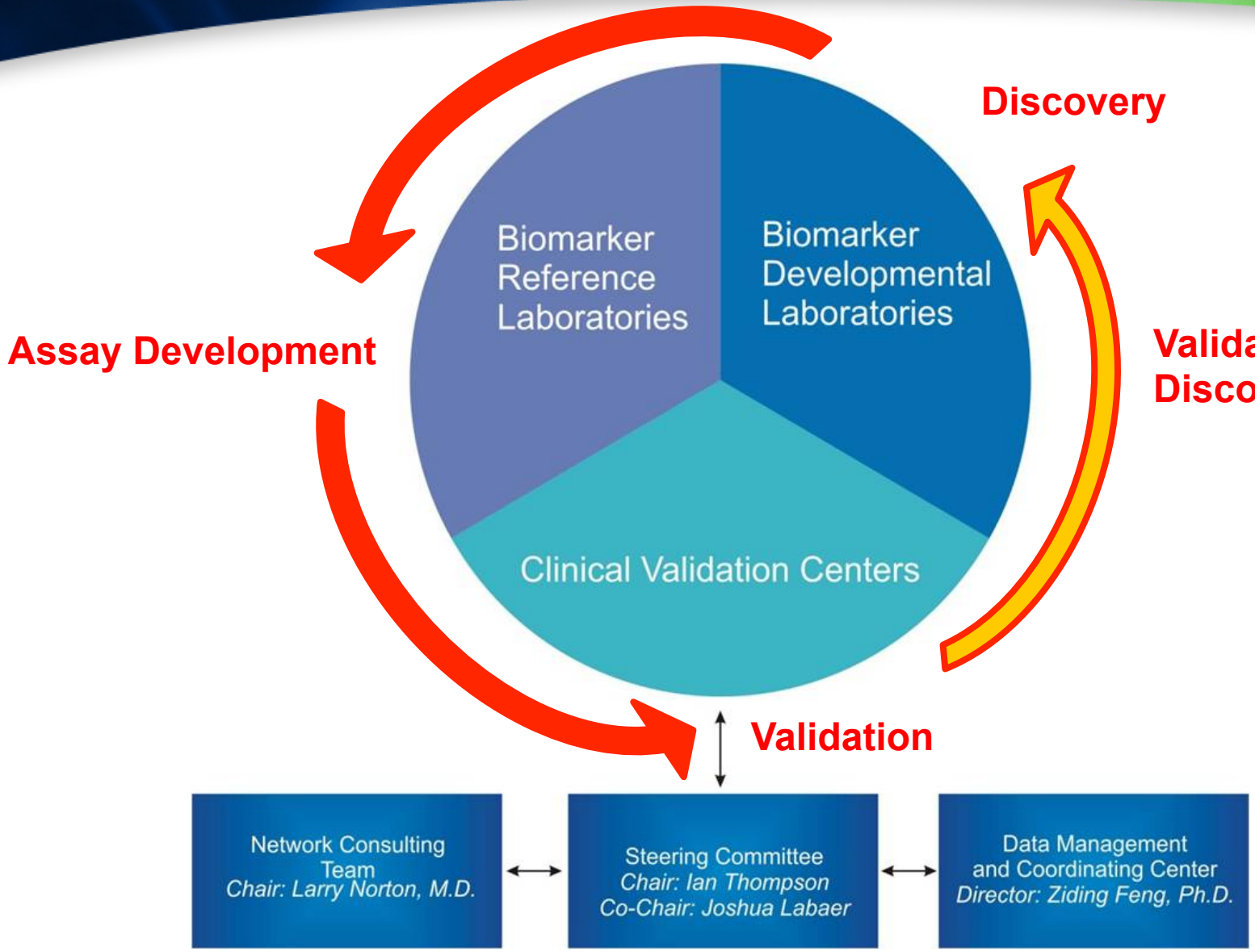
# EDRN Program Objectives

Early Detection Research Network

- Establish an investigator-initiated infrastructure to support development and validation of early detection biomarkers and markers of progression
- Foster interaction between academic, clinical and industry leaders
- Standardize biomarker validation criteria
- Develop a quality assurance program
- Bring biomarkers to clinical use

# Organization of EDRN

Early Detection Research Network



# Biomarker Developmental Laboratories: Scope

Early Detection Research Network

Biomarker Developmental Laboratories (BDLs) conduct discovery, development, characterization and testing of new, or the refinement of existing, biomarkers and biomarker assays for:

- Risk assessment
- Molecular Detection
- Molecular Diagnosis and Prognosis of Early Cancer

# Clinical Validation Centers: Scope

Early Detection Research Network

- Clinical Validation Centers (CVCs) conduct biomarker validation studies
- Partner with other networks with available biospecimens for biomarker validation (e.g., NCTN, Cohort Consortium, HMOs)
- Serve as a Collaborative Resource for the Network
- Partner with EDRN Biomarker Developmental Laboratories (BDLs) and EDRN Reference Laboratories (BRLs)

# Biomarker Reference Laboratories: Scope

Early Detection Research Network

Biomarker Reference Laboratories (BRLs) serve as Network resources for the validation of biomarkers for clinical or laboratory use. Their responsibilities include:

- Testing of candidate biomarkers
- Assay design and development
- Assay optimization and refinement
- Assay methods and protocol standardization

# Data Management and Coordinating Center: Scope

Early Detection Research Network

- Network Coordination
- Data Management and Protocol Development
- Validation Infrastructure and Services
- EDRN Core Fund Management

# Partnering Organizations


- National Institute of Standards and Technology
- Center for Prostate Disease Research, DOD
- Pacific Northwest National Laboratory, DOE
- Jet Propulsion Laboratory, NASA
- Canary Foundation of America
- Lustgarten Foundation N.Y.
- International collaborations:

  China (C-EDRN), Cancer Research-UK, Turkey, Japan, Chile, Israel
- Industry (15 active)
- Associate Members (>200)

# EDRN Milestones:
## From Structure to Process to Outcomes

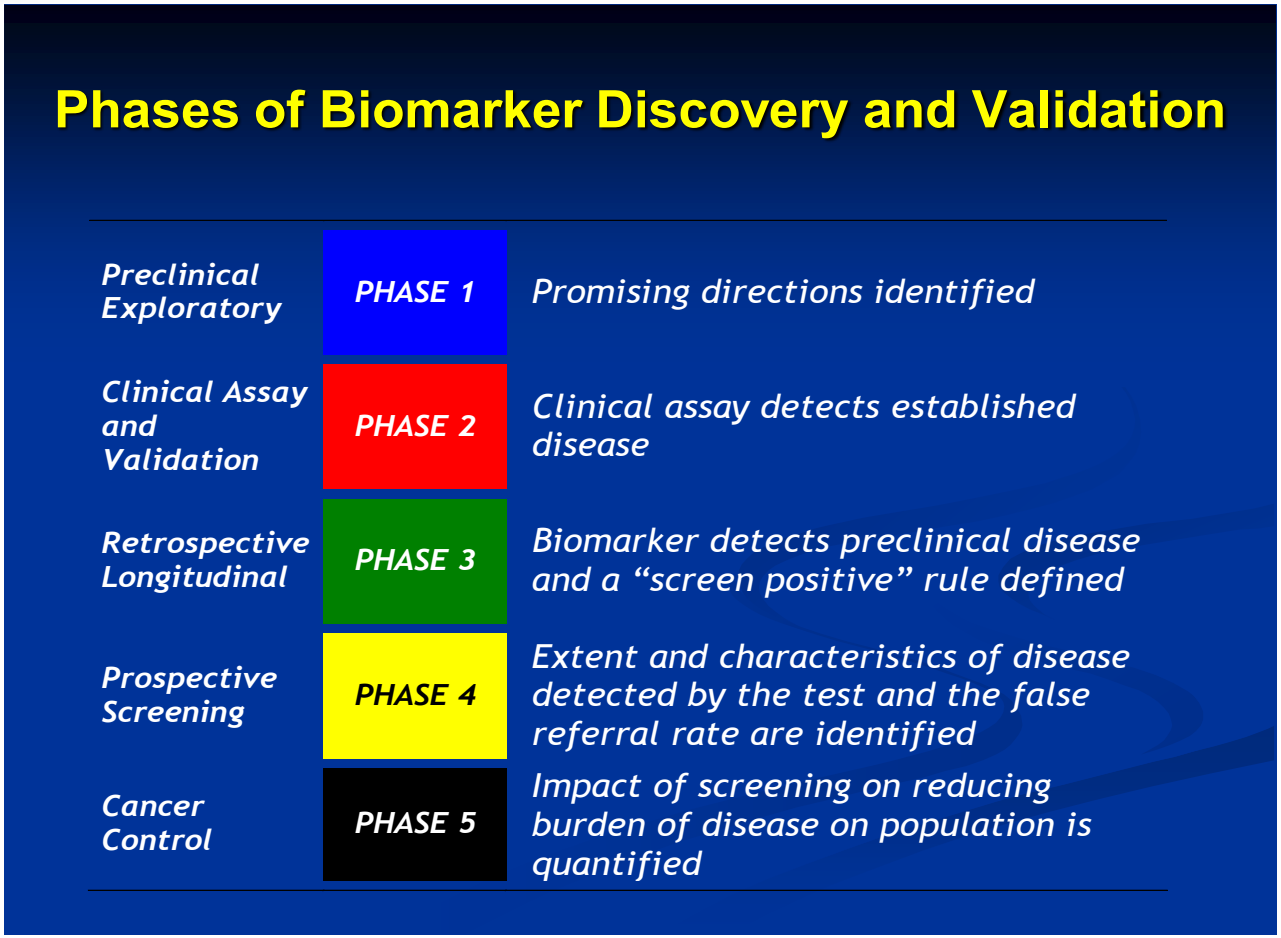
Early Detection Research Network

| 2000-2005<br>Coordinate, Communicate and Collaborate | 2005-2010<br>Learn, Improve and Deliver | 2010-Present<br>Productivity, Outcome and Dissemination |
|---|---|---|
| ✓ 33 Principal Investigators | ✓ 45 Principal Investigators | ✓ 57 Principal Investigators |
| ✓ Steering Committee Attendance: 85; Workshop 300 | ✓ Steering Committee Attendance: 120; Workshop 300 | ✓ Steering Committee Attendance: 150; Workshop: 350 |
| ✓ Associate Membership Program Initiated; 32 Associate Members | ✓ 123 Associate Members | ✓ 231 Associate Members |
| ✓ EDRN-Gordon Research Tie-up (2002, 2003) | ✓ 2 EDRN-Gordon Research Workshops (2005, 2007) | ✓ DCP and AFP-L3 FDA Approved for Liver Cancer and ROMA for Ovarian Cancer |
| ✓ Initiated EDRN-Human Proteome Organization Plasma Proteome Project | ✓ MOUs signed With Canary Foundation, Lustgarten Foundations, Turkey | ✓ proPSA and PCA-3 FDA Approved for Prostate Cancer |
| ✓ Guidelines for Biomarker Discovery and Validation | ✓ OVA1 FDA Approved | ✓ 11 CLIA-approved Diagnostic Tests |
| ✓ Project Management Tools Created | ✓ EDRN-FDA Educational Biennial Workshop | ✓ 10 Clinical Reference Sets completed and stored at Frederick, MD |
| ✓ Multi-center Trial Informatics Infrastructure created, verified | ✓ EDRN-NIST Workshop on Standards | ✓ IRB Approvals Monitored: 216; 200 Protocols;100 MTAs |
| ✓ Virtual Specimen Bank Established | ✓ IRB approvals monitored: About 80 sites | |
| ✓ IRB Approvals Monitored: 38 sites | | |

# Study Designs for Biomarker Development

Early Detection Research Network

**PRoBE Study Design:**
**P**rospective-Specimen-Collection, **R**etr**o**spective-**B**linded-**E**valuation




**Phases of Biomarker Development for Early Detection of Cancer**
Margaret Sullivan Pepe et al.
J Natl Cancer Inst, Vol. 93, No. 14, July 18, 2001

**Pivotal Evaluation of the Accuracy of a Biomarker Used for Classification or Prediction: Standards for Study Design**
Margaret Sullivan Pepe et al.
J Natl Cancer Inst 2008; 100:1432-1438

# Salient Features of EDRN

Early Detection Research Network

- Provide **Integrated Infrastructure**
- **Build Resources** for Biomarker Research
- **Establish Standardized Criteria** for Biomarker Discovery and Validation
- **Quality Assurance** Programs
- Ensure Research **Reproducibility**
- Improve Screening and Diagnostic **Tests for Common Clinical Dilemmas**

# Building Resources for Clinical Studies

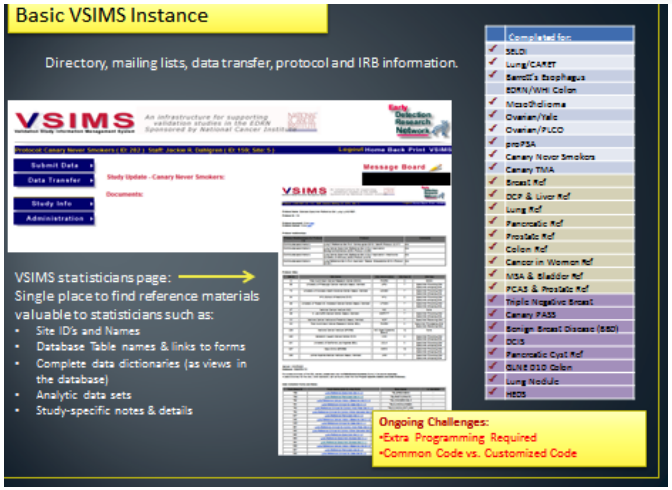
Early Detection Research Network

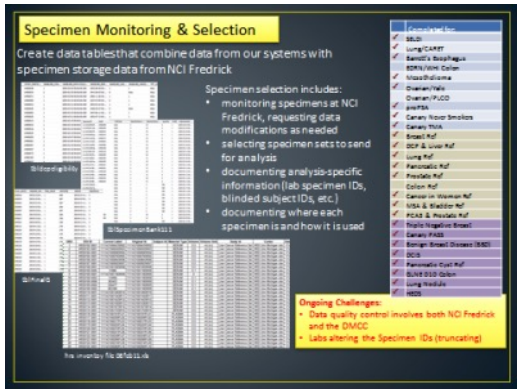
- Platform for multi-center biomarker validation studies
- Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories to develop and test assays using GLP and GMP
- Centralized statistical center for data analysis and informatics infrastructure to share data
- Mechanism for biomarker triaging prior to large, expensive validation studies (use of Reference Sets)
- >100,000 clinically-annotated biospecimens using common data elements (CDEs)

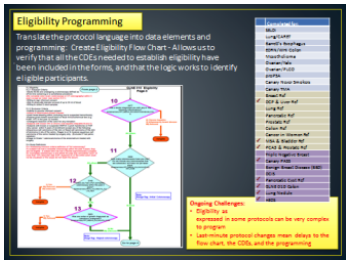
# Building Resources for Clinical Studies:
## Informatics and Bioinformatics (Jet Propulsion Lab)

Early Detection Research Network

- VSIMS for multicenter validation studies
- eSIS for study management
- ERNIE for Virtual Specimen Banks (tracks >100,000 biospecimens)
- Prioritized Biomarker Database
- >2600 Common Data Elements
- Validation data collected through LabCAS (proteomic and genomic data) and eCAS
- Crowd-sourcing being considered on stored data




http://edrn.nci.nih.gov/informatics/informatics

# Highlights of this Funding Opportunity Announcement (FOA)

Early Detection Research Network

## Biomarker Development Laboratories ( RFA-CA-16-009 U01)

The application in response to this FOA must be focused on cancers of the breast, prostate and other genitourinary organs, and lung. In addition, cancers with rapidly rising incidence rates, e.g., endometrial, hepatocellular, kidney, thyroid, oropharyngeal cancers, and/or cancers with unique etiology, e.g., mesothelioma, will be responsive.

All of the components of EDRN are funded through the Cooperative Agreement Mechanisms in which there is substantial involvement of the NCI staff

# General Requirements of this FOA

Early Detection Research Network

- Adhere to FOA-specific scope, specific requirements, page limitations, and other details
- Describe study designs
- Describe statistical analyses
- Collaborate with cohort, consortia, HMOs, Cooperative Groups, and other relevant entities for a shovel-ready biospecimen collection for development of biomarkers
- Pay attention to review criteria when preparing your application
- Describe licensing and IP plan, if applicable

# Purpose of this FOA

Early Detection Research Network

This FOA solicits applications for EDRN Biomarker Developmental Laboratories (BDLs) to discover and develop biomarkers and molecular and cellular signatures for risk assessment, detection, and diagnosis and prognosis of early cancers.

# Key Responsibilities of BDLs in the Five-Phase Development of Biomarkers

Early Detection Research Network

| | | |
|---|---|---|
| ***Preclinical Exploratory*** | ***PHASE 1*** | *Promising directions identified* |
| ***Clinical Assay and Validation*** | ***PHASE 2*** | *Clinical assay detects established disease* |
| ***Retrospective Longitudinal*** | ***PHASE 3*** | *Biomarker detects preclinical disease and a "screen positive" rule defined* |
| ***Prospective Screening*** | ***PHASE 4*** | *Extent and characteristics of disease detected by the test and the false referral rate are identified* |
| ***Cancer Control*** | ***PHASE 5*** | *Impact of screening on reducing burden of disease on population is quantified* |

Pepe, SM. J Natl Cancer Inst. 2001 Jul 18;93(14):1054-61.

# Examples of Biomarker Discovery Research

Early Detection Research Network

- Development of molecular signatures based on **integrated 'omics' approaches** to assess risk; to identify pre-cancerous lesions and early stage cancer; and to identify of cancers that are likely to progress.

- Development of biomarkers in preclinical specimens to **discriminate between screen-detected aggressive lesions and indolent or slow-growing lesions** to reduce the burden of overdiagnosis and overtreatment.

- Development of biomarkers for **risk stratification;** improve risk stratification by improving pathological classification, especially of early lesions.

- Molecular signatures for risk of and early stage disease due to **infectious agents, pathogens**, or environmental agents.

# Examples of Biomarker Discovery Research (Cont'd)

Early Detection Research Network

- Development of **integrated approach** based on **imaging modalities and molecular/'omic' biomarkers** for risk assessment, early detection, diagnosis and early prognosis.

- Effectively delineate disease **genotypes** and **phenotypes of pre-cancerous and cancerous lesions that are likely to progress**.

- Determine the potential of **perturbed network- and pathway-based biomarkers**.

# Biomarker Developmental Laboratories: Expectations

Early Detection Research Network

- Laboratory scientists with extensive biomarker research experience and experience with knowledge and principles of biomarker discovery
- Biomarkers addressing specific clinical question(s) in the realm of early detection (Phase 1 and Phase 2)
- Discovery based on EDRN's five-phase biomarker development criteria and PRoBE or a similar study design
- Availability of quality specimens for discovery as opposed to "convenience samples"
- Robust study design and appropriate statistical approach to minimize false discovery (plan to adjust for multiplicity, plan to minimize chance, bias, overfitting, etc.)
- Decision criteria for triaging candidate biomarkers
- Achievable timeline of proposed research
- Collaboration to complement expertise and resources; IP and licensing plan to ensure that collaboration is not affected

# Page Limitations

Early Detection Research Network

All page limitations described in the SF424 Application Guide and the Table of Page Limits must be followed, with the following exception:

For this specific FOA, the Research Strategy must not exceed 30 pages.

# Requirements and Key Components for a BDL

Early Detection Research Network

**Facilities and Resources**

- Specialized or unique resources important for achieving objectives
- PDs/PIs must have their own research laboratories and demonstrate they have expertise in the technologies they propose to use

**Key Personnel (include or have access to)**

- Pathologist – expertise in your disease focus
- Clinical epidemiologist/biostatistician – understands PRoBE study design, power calculations for a strong study design
- A designated Project Manager who will be the main point-of-contact regarding the details and activities of the study

# Budget

Early Detection Research Network

- Direct costs may not exceed $250K/yr for single-PI or $400K/yr for multi-PD/PI awards, including the 30% set-aside.
- The lead PD/PI must commit a minimum of 1.8 person-months effort per year. For multiple PD/PI awards, the other PDs/PIs must devote a minimum of 1.2 person-months effort per year.
- Set aside 30% of the annual budget for Network collaborative studies from Year 1 onward. Release of these funds must be reviewed by the EDRN Steering Committee and approved by NCI.
- Travel and per diem expenses for PD/PI and an additional senior investigator to attend:
    - Planning (Orientation) and a Steering Committee Meeting in the first year (two meetings)
    - Two Steering Committee Meetings per year
    - One Network Workshop or Symposium every 18 months

# Budget (Cont'd)

Early Detection Research Network

## An example of 1st year restricted travel budget for 2 PIs attending 2 Meetings

**C. Equipment Description**

List items and dollar amount for each item exceeding $5,000

| Equipment item | Funds Requested ($) |
|---|---|
| | |

Additional Equipment: [ ] Add Attachment | Delete Attachment | View Attachment

Total funds requested for all equipment listed in the attached file:

Total Equipment:

**D. Travel**

| | | Funds Requested ($) |
|---|---|---|
| 1. | Domestic Travel Costs ( Incl. Canada, Mexico and U.S. Possessions) (2 PIs x 2 Mtgs x $2,000) | 8,000 |
| 2. | Foreign Travel Costs | |
| | Total Travel Cost | 8,000 |

**E. Participant/Trainee Support Costs**

| | | Funds Requested ($) |
|---|---|---|
| 1. | Tuition/Fees/Health Insurance | |
| 2. | Stipends | |
| 3. | Travel | |
| 4. | Subsistence | |
| 5. | Other | |
| | Number of Participants/Trainees | Total Participant/Trainee Support Costs |

**All applicants** must set aside 30% of their budget from the 1st year onward for Network collaborative studies.

- 30% of the $400K (direct cost) = $120K (direct cost)
- The remaining budget, $400K - $120K = **$280K** (direct cost) will be used towards the proposed BDL studies.

**F. Other Direct Costs**

| | | Funds Requested ($) |
|---|---|---|
| 1. | Materials and Supplies | |
| 2. | Publication Costs | |
| 3. | Consultant Services | |
| 4. | ADP/Computer Services | |
| 5. | Subawards/Consortium/Contractual Costs | |
| 6. | Equipment or Facility Rental/User Fees | |
| 7. | Alterations and Renovations | |
| 8. | Network Collaborative Studies (30% of direct costs) | 120,000 |
| 9. | | |
| 10. | | |
| | Total Other Direct Costs | 00,000 |

**G. Direct Costs**

| | Funds Requested ($) |
|---|---|
| Total Direct Costs (A thru F) | 400,000 |

**H. Indirect Costs**

| Indirect Cost Type | Indirect Cost Rate (%) | Indirect Cost Base ($) | Funds Requested ($) |
|---|---|---|---|
| | | | |

Total Indirect Costs

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)

**I. Total Direct and Indirect Costs**

| | Funds Requested ($) |
|---|---|
| Total Direct and Indirect Institutional Costs (G + H) | |

**J. Fee**

Funds Requested ($)

**K. Budget Justification**

(Only attach one file.) Add Attachment | Delete Attachment | View Attachment

# Organization of Application: PHS 398 Research Plan

Early Detection Research Network

All standard SF424 instructions for PHS 398 Research Plan must be followed along with the additional items noted below:

## Specific Aims

In addition to a brief description of the specific aims and approach(es) to be employed, applicants must outline the scope of the proposed research and its relevance to a specific unmet clinical need in the management of human malignancies.

## Research Strategy

***Sub-section A*: Overview** – Team structure, relevant partnerships or collaborations, data & resource sharing

***Sub-section B*: Previous Accomplishments** – Related to biomarker discovery

***Sub-section C*: Research Project** – What you propose to do

***Sub-section D*: Project Management Plan**

1. Timeline
2. Milestones (quantifiable)
3. Decision-tree scheme (when to stop or continue with biomarkers)

# Organization of Application: PHS 398 Research Plan (Cont'd)

Early Detection Research Network

## Multiple PD/PI Leadership Plan

In addition to following standard instructions, applicants should explain how the multiple PDs/PIs will divide their scientific responsibilities in terms of focus on different platforms for biomarker discovery and development. In this context, it is expected that each PD/PI will be responsible for a different platform (although overlap in types of tumors of focus across PDs/PIs is acceptable).

## Letters of Support

In addition to standard items, provide letters of commitment for resources and/or technology made available by industry partners involved in the proposed research.

## Resource Sharing Plan

1. Specimen Sharing
2. Intellectual Property Management Plan

# Receipt and Other Schedules

Early Detection Research Network

- Letter of Intent Due Date: April 23, 2016
- Application Due Date: May 23, 2016 (by 5:00 PM local time of applicant organization)
- Peer Review Date: July 2016
- Advisory Council Review: August 2016
- Earliest Anticipated Start Date: September 2016

# Summary

Early Detection Research Network

- Propose biomarker Phase 1/Phase 2 biomarker discovery studies addressing unmet clinical needs
- Highlight key personnel, incorporation of PRoBE design, relevant statistical considerations of study design, and measurable research milestones
- Collaboration with national networks and NCI-supported programs for access to high quality specimens
- Access to specific patient populations for prospective specimen collections
- Partnership with other EDRN components (visit www.cancer.gov/edrn )
- Project management plan with timelines and quantitative milestones
- Resource and data sharing plan, and Intellectual Property management plan

# Application Checklist

Early Detection Research Network

- Is application organized per instructions in the RFA?
- Have the review criteria been addressed in the proposal?
- Are the proposed specific aims achievable in a given time frame?
- Has collaboration been established and partners on board?
- Has a contact PI been identified for multi-PI proposal and communication and management plan developed?
- Have the special requirements been followed in developing the proposal, e.g., page limit, team structure, study designs, etc.?

# NCI PD Contacts

Early Detection Research Network

- Jacob Kagan, M.Sc., Ph.D. (Prostate and Other Urological Cancers)
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- Karl Krueger, Ph.D. (Lung and Upper-Aerodigestive Cancers, Glycomics)
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# Thank you